EXPRESS MAIL NO.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Charles L. Magness and Shawn P. Iadonato
Application No.	:	09/707,576
Filed	:	November 6, 2000
For	:	SYSTEM AND METHOD FOR SELECTIVELY CLASSIFYING A POPULATION

Examiner	:	Anna Skibinsky
Art Unit	:	1631
Docket No.	:	55382-3
Date	:	December 15, 2006

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Affidavit of Cammie Lesser, M.D., Ph.D. under 37 C.F.R. § 1.132

I, Cammie Lesser, M.D., Ph.D. being duly sworn, say:

1. I am an internationally recognized scientist and I am employed as Assistant Professor at Massachusetts General Hospital/Harvard Medical School in Boston, Massachusetts. I received a Bachelors Degree in Biochemistry from Brown University, a Ph.D. degree in Biochemistry in 1993 from the University of California at San Francisco, and an M.D. degree in 1995 from the University of California at San Francisco.

2. I am an author or co-author of several peer-reviewed research articles and I have been invited to give presentations on my research at national and international

meetings. Prior to joining Massachusetts General Hospital/Harvard Medical School, I was a medical resident at the University of Washington. My curriculum vitae is attached as Exhibit 1.

3. On information and belief, claims of the present application have been rejected under 35 U.S.C. § 112, first paragraph. According to pages 9-10 of the Office Action dated June 16, 2006, claims 1-10, 14-26, 28, 31-44 and 46-55 fail to comply with the enablement requirement because allegedly there is "undue experimentation required to go from the classification results achieved by implementing the invention to drug target identification without some prior knowledge of a relationship between a potential target and a biological condition as claimed." It is my opinion that the methods described in the application support the enablement of the claimed invention. As discussed below, I conclude that undue experimentation would not be required to identify a drug target using the methods of the invention.

4. I am aware that it is possible and routine to identify a mutation without knowledge of the underlying disease mechanism, and to determine whether that mutation corresponds to phenotypic characteristics of a population such as the ARU group. In the context of the claim language and the patent specification, I understand that a population "at risk" could be a population exposed to an infectious agent, a subpopulation "at risk and affected" would be a population exhibiting a phenotypic trait, such as evidence of infection, and that a subpopulation "at risk and unaffected" would be a population expected to have the disease on the basis of history of exposure, yet not exhibiting phenotypic evidence of the infection (*i.e.* symptomatic, serum antibodies, *etc.*). I am also aware that the phenotypic definition of "at risk unaffected" varies from one biological condition to another and this definition allows the breadth of applicability of the present methods to conditions other than infectious disease.

5. As a medical doctor, I am aware of the procedures and requirements for identifying matched individuals for conducting risk analysis of infections and other diseases. In my opinion, identifying "at risk unaffected" and "at risk affected"

populations, and obtaining biological samples, such as blood samples, is routine and need not be time-consuming. Such samples are routinely obtained in the course of medical examination and diagnosis.

6. Based on my scientific knowledge of molecular genetics, I am familiar with the methods routinely used to identify mutations in genes and to correlate these mutations with functional effects, such as modification of protein amino acid sequence. I also appreciate how the identification of such functional genetic variations between ARA and ARU groups directly identifies the gene containing the genetic variations as a drug target. Anyone of ordinary skill in the field of molecular genetics would have a comparable level of familiarity and expertise.

7. On information and belief, the Office Action at page 8, lines 5-7, alleges that "applicants have not described how to identify where the genetic variation associated with the disease exists." The Office Action at page 8, line 21 through page 9, line 2, in a similar argument further alleges "it is not disclosed how the relevant polynucleotide is detected. Additionally, how the functional coding region carrying the genetic difference of interest is located." I disagree with these allegations. Applicants describe in the specification between page 10, line 22 and page 13 line 5, methods for detecting mutations and statistically associating those mutations with the ARA group relative to a control group. Using well-known methods of sequence analysis, mutation identification and statistical genetics, it is entirely feasible and within ordinary skill in this art to identify a genetic difference that correlates with the affected versus unaffected phenotype.

8. On information and belief, the Office Action at page 10, lines 14-15, alleges that "identification of a drug target requires the sorting out of 1000's of targets present in most organisms." I disagree with this statement. It is highly unlikely that few, if any, drug targets have been identified by "sorting out 1000's of targets present in most organisms."

9 On information and belief, what applicants have disclosed and claimed is not the traditional method of target and drug discovery. In fact, an advantage of the present methods is that they are the opposite of traditional methods. The present methods allow identification of a drug target by comparison of the ARA and ARU groups rather than by traditional approaches to drug target discovery. Many of the risk analyses and genetic comparisons outlined by the present methods are also amenable to computer automation. Thus the present methods provide a very effective short-cut to drug target discovery, and allow a researcher to identify relevant differences between the ARA and ARU subjects. The identification of the observed genetic difference (*e.g.* point mutation, deletion, insertion) between the "at risk unaffected" and "at risk affected" groups leads directly to identification of a target. The effect of the observed genetic difference on target function also leads the researcher to the type of required therapeutic intervention (e.g. protein replacement therapy versus antagonistic small molecule).

10. Because the target is identified in humans, the method of the invention provides at least two other differences from and advantages over traditional drug target identification. First, it circumvents much of the laboratory animal experimentation otherwise performed to identify a target. Second, because the at risk unaffected population is healthy, the method teaches development of a treatment that mimics the effect of the protective mutation in the ARU population. As such, a treatment that mimics the mutation is less likely to have the side effects that so often derail an otherwise promising drug treatment, sometimes when clinical trials are very advanced.

11. In conclusion, I am a person of ordinary skill in this art. It is within my ability to understand and follow the claimed methods. For any disease in which the phenotype is related to a genetic difference, I would expect the claimed methods to allow someone of my skill level to discover that difference, and to correlate it with a gene-specific effect, such as a protein modification. That gene–specific effect in turn will correlate with the phenotypic difference between "at risk unaffected" (ARU) and "at risk affected" (ARA) individuals. This information will allow one skilled in the art to

design a treatment to mimic the protective phenotype of the "at risk unaffected" individuals.

I further declare that all statements made herein of my own knowledge are true and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

Cammie Lesser, M.D., Ph.D.

Commonwealth of Massachusetts)
) ss.
County of Middlesex)

On this 15 day of December, 2006, before me, a Notary Public in and for the Commonwealth and County aforesaid, personally appeared Cammie Lesser, M.D., Ph.D., to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and she acknowledged the same to be her free act and deed.

Notary Public

Commission expires 1/19/2012

STACY B. SARNO, ESQ.
Notary Public
COMMONWEALTH OF MASSACHUSETTS
My Commission Expires January 19, 2012

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Cammie Lesser	Assistant Professor
eRA COMMONS USER NAME	
cflesser	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Brown University	Sc.B.	1985	Biochemistry
University of California, San Francisco	Ph.D.	1993	Biochemistry
University of California, San Francisco	M.D.	1995	Medicine

NOTE: The Biographical Sketch may not exceed four pages. Items A and B (together) may not exceed two of the four-page limit. Follow the formats and instructions on the attached sample.

A. Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

1995-1997 Medical Resident, Department of Medicine, University of Washington, Seattle, WA
1997-2001 Senior Fellow, Division of Allergy and Infectious Diseases, University of Washington, Seattle, WA
2001-2003 Acting Instructor, Department of Medicine, Division of Allergy and Infectious Diseases, University of Washington, Seattle, WA
2003- Assistant Professor, Department of Medicine, Division of Infectious Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Honors/Awards

2004 Invited Speaker, Cold Spring Harbor Functional Genomics of Host Pathogen Interactions Meeting, Cambridge, England
2003 Recipient of Charles E. Culpeper Medical Scholarship
2003 Invited Speaker, Cold Spring Harbor Meeting on Microbial Pathogenesis and Host Response
2000 Invited Spearker, Gordon Conference on Bacterial Toxins and Pathogenesis
1999 Recipient of Howard Hughes Postdoctoral Fellowship
1999 Recipient of Pfizer Postdoctoral Fellowship for Infectious Diseases
1993 Journal Article (Lesser, CF and Guthrie, C. Science 262,1982 (1993)) chosen as "Hot Paper" by "The Scientist."
1985 Magnum Cum Laude, Brown University
1985 Academic Acheivement Award from the Division of Biology and Medicine, Brown University
1985 Senior Thesis Prize in Biochemistry form Division of Chemistry, Brown University
1985 Academic Honors in Biochemistry, Brown University

B. Selected peer-reviewed publications (in chronological order). Do not include publications submitted or in preparation.

1. Leong, J.M., Nunes-Duby, S., **Lesser, C.F.**, Youderin, P., Susskind, M.M. and Landy, A. (1984). Site-specific recombination systems of phages Ø80 and P22: binding sites of integration host factor and recombination-induced mutations. Cold Spring Harbor Symposia on Quantitative Biology, 49, 707-14.
2. Leong, J.M., Nunes-Duby, S., **Lesser, C.F.**, Youderin, P., Susskind, M.M. and Landy, A. (1985). The Ø80 and P22 attachment sites. Primary structure and interaction with *Escherichia coli* integration host factor. Journal of Biological Chemistry 260 (7), 4468-77.
3. Leong, J.M., Nunes-Duby, S., Oser, A.B., **Lesser, C.F.**, Youderin, P., Susskind, M.M. and Landy, A. (1985). Structural and regulatory divergence among site-specific recombination genes of lambdoid phage. Journal of Molecular Biology 189 (4), 603-616.
4. Andrews, D.W., Perara, E., **Lesser, C.F.** and Lingappa, V.R. (1988). Sequences beyond the cleavage site influence signal peptide function. Journal of Biological Chemistry 263 (30), 603-16.
5. **Lesser, C.F.** and Guthrie, C. (1993). Mutational analysis of pre-mRNA splicing in *Saccharomyces cerevisiae* using a sensitive new reporter gene, CUP1 . Genetics 133 (4), 851-63.
6. **Lesser, C.F.** and Guthrie, C. (1993). Mutations in U6 snRNA that alter splice site specificity: implications for the active site. Science 262 (5142), 1982-8.
7. **Lesser, C.F.**, Scherer, C.A and Miller, S.I. (2000). Rac, Ruffle and Rho: Orchestration of *Salmonella* ruffling. Trends in Microbiology 8(4), 151-2.
8. **Lesser, C.F.** and Miller, S.I. (2001) Expression of microbial virulence factors in *Saccharomyces cerevisiae* models mammalian infection. EMBO 20 (8), 1840-9.
9. **Lesser, C.F.** and Miller, S.I. (2001) Tractable *Saccharomyces cerevisiae* is model system for studying pathogenic bacterial proteins: introducing bacterial virulence proteins into yeast provides valuable insights about their interactions with host components. ASM News. 67(9), 448-455.
10. Gottlieb, G.S., **Lesser, C.F.**, Holmes K.K. and Wald,A. (2003) Disseminated Sporotrichosis associated with treatment with immunosuppressants and TNF alpha antagonists. CID 37(6):838-40.

Reviews, Chapters, and Editorials,

1. **Lesser CF**, Scherer CA, Miller SI. Rac, Ruffle and Rho: Orchestration of *Salmonella* ruffling. Trends in Microbiology 2000; 8(4), 151-2.
2. **Lesser CF**, Miller SI. Salmonellosis. In *Harrison's Principles of Internal Medicine*, Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. McGraw-Hill; 2001. 975-8.
3. **Lesser CF**, Miller SI. Salmonellosis. In *Harrison's Principles of Internal Medicine*, Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. McGraw-Hill; 2004..